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Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium

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ABSTRACT

BACKGROUND: The profile of cortical neuroanatomical abnormalities in schizophrenia is not fully understood, despite hundreds of published structural brain imaging studies. This study presents the first meta-analysis of cortical thickness and surface area abnormalities in schizophrenia conducted by the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) Schizophrenia Working Group.

METHODS: The study included data from 4474 individuals with schizophrenia (mean age, 32.3 years; range, 11–78 years; 66% male) and 5098 healthy volunteers (mean age, 32.8 years; range, 10–87 years; 53% male) assessed with standardized methods at 39 centers worldwide.

RESULTS: Compared with healthy volunteers, individuals with schizophrenia have widespread thinner cortex (left/right hemisphere: Cohen's $d = -0.530/-0.516$) and smaller surface area (left/right hemisphere: Cohen's $d = -0.251/-0.254$), with the largest effect sizes for both in frontal and temporal lobe regions. Regional group differences in cortical thickness remained significant when statistically controlling for global cortical thickness, suggesting regional specificity. In contrast, effects for cortical surface area appear global. Case-control, negative, cortical thickness effect sizes were two to three times larger in individuals receiving antipsychotic medication relative to unmedicated individuals. Negative correlations between age and bilateral temporal pole thickness were stronger in individuals with schizophrenia than in healthy volunteers. Regional cortical thickness showed significant negative correlations with normalized medication dose, symptom severity, and duration of illness and positive correlations with age at onset.

CONCLUSIONS: The findings indicate that the ENIGMA meta-analysis approach can achieve robust findings in clinical neuroscience studies; also, medication effects should be taken into account in future genetic association studies of cortical thickness in schizophrenia.

Keywords: Cortical, Imaging, Meta-analysis, Schizophrenia, Surface area, Thickness

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Brain structural abnormalities are widely reported in schizophrenia, but there is no published meta-analysis reporting effect sizes for cortical thickness and surface area abnormalities and their relationships to clinical features of the disease. Several hundred studies have reported on cortical thickness and surface area abnormalities in schizophrenia, but it is difficult to meta-analyze published results, as they lack a standard format to ease comparisons and are based on atlas (1) or vertex-wise (2) approaches using a variety of methods (3–9). To address these issues, the Schizophrenia Working Group within the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis; http://enigma.ini.usc.edu) (10–12) consortium brings together schizophrenia researchers from all over the world to jointly conduct large-scale imaging and imaging/genetics meta-analyses using standardized methods.

This meta-analysis focuses on regional cortical thickness and surface area rather than volume, based on evidence that they are influenced by separate sets of genes (13,14). Cortical thickness and surface area abnormalities have been reported in individuals with chronic (1,15–17), short- or medium-duration (18), first-episode (19–24), child-onset (25,26), adolescent-onset (27), and antipsychotic-naïve (28–30) schizophrenia; individuals with nonclinical psychotic symptoms (31); and individuals at clinical high risk for psychosis (32–39).

We previously reported effect sizes for deep brain structure volume abnormalities based on 15 samples worldwide, including brain imaging data from 2028 individuals with schizophrenia and 2540 healthy volunteers (40); findings were replicated in an independent cohort using similar methods (41). Here we report Cohen's *d* effect sizes comparing regional cortical thickness and surface area between 4474 individuals with schizophrenia and 5098 healthy volunteers, and partial correlation effect sizes with continuous clinical measures based on 39 worldwide samples. Based on prior work, we hypothesized that individuals with schizophrenia, compared with healthy volunteers, show widespread cortical thickness and surface abnormalities that are most prominent in frontal and temporal lobe regions (15) and that show significant associations with age at onset or duration of illness (42), symptom severity (43–48), and antipsychotic medication use (49–51).

METHODS AND MATERIALS

Study Samples

Via the ENIGMA Schizophrenia Working Group, 39 worldwide, cross-sectional study samples totaling 9572 participants, including 4474 individuals with schizophrenia and 5098 healthy volunteers, contributed to the analysis (Tables S1a and S1b and Figure S1 in Supplement 1). Sample-size weighted mean (range) age across samples was 32.3 (21.2–43.6) years for individuals with schizophrenia and 34.5 (21.8–43.9) years for healthy volunteers. Patient and control samples were on average 65% (44–100) and 54% (36–100) male. Weighted mean age at onset and duration of illness across the samples were 23.4 (20.0–35.6) years and 10.5 (0.6–20.2) years. Weighted mean Positive and Negative Syndrome Scale (PANSS) (52) total, negative, and positive scores across the samples were 68.1 (43.0–90.2), 21.9 (10.0–22.9), and 16.4 (10.6–22.6); weighted mean Scale for the Assessment of Negative Symptoms (53) and Scale for the Assessment of Positive Symptoms (54) scores were 20.5 (5.5–33.0) and 19.2

(9.0–32.3), respectively. For samples that recorded current antipsychotic type and/or dose, numbers (percentages) of patients on second-generation (atypical), first-generation (typical), both second-generation and first-generation, or no (unmedicated) antipsychotic medications were 2236 (66%), 447 (13%), 265 (8%), and 425 (13%), and sample-size weighted mean chlorpromazine dose equivalent, based on Woods' calculations (www.scottwilliamwoods.com/files/Equivtext.doc), was 399 (167–643). Each study sample was collected with participants' written informed consent approved by local institutional review boards.

Image Acquisition and Processing

All sites processed T1-weighted structural brain scans using FreeSurfer (9) (http://surfer.nmr.mgh.harvard.edu) and extracted cortical thickness and surface area for 70 Desikan-Killiany (DK) atlas regions (55) (34 regions per hemisphere + left and right hemisphere mean thickness or total surface area) (Table S3 in Supplement 1). Number of scanners, vendor, strength, sequence, acquisition parameters, and FreeSurfer versions are provided in Table S2 in Supplement 1. ENIGMA's quality assurance protocol was performed at each site before analysis and included visual checks of the cortical segmentations and region-by-region removal of values for segmentations found to be incorrect (http://enigma.usc.edu/protocols/imaging-protocols) (Table S2 in Supplement 1). Histograms of all regions' values for each site were also computed for visual inspection.

Statistical Meta-analyses

Group differences for DK atlas regions within each sample were examined using univariate linear regression (R linear model function lm; R Foundation for Statistical Computing, Vienna, Austria) predicting left and right DK atlas region cortical thickness or surface area with group (individuals with schizophrenia, healthy volunteers), gender, and age (model A). To further assess whether group differences in cortical thickness and surface area showed regional specificity, analyses were repeated including global mean cortical thickness and total cortical surface area as covariates, respectively (model B). To test for differential gender or age effects between groups, we also included models with group-by-gender (model C) or group-by-age interaction terms (model D). Significant interactions were further explored through within-group analyses. Medication effects were examined through between-group comparisons of individuals with schizophrenia on second-generation (atypical), first-generation (typical), both second-generation and first-generation, or no (unmedicated) antipsychotic medications and healthy volunteers with gender and age included as covariates; only contrasts with a minimum of 5 subjects per group within site were included in these analyses to enable variance estimation. In patients, relationships were examined between regional cortical measures and several continuous variables, including age at onset; duration of illness; chlorpromazine equivalent antipsychotic medication dose; and total, positive, and negative symptom severity. These partial correlation analyses included age and gender as covariates. Analysis of multiscanner studies (ASRB, FBIRN, MCIC, Osaka, UPENN) included binary dummy covariates for n-1 scanners. Sites conducted analyses of their sample's individual subject data using R code created within the ENIGMA collaboration. Random-effects meta-analyses of Cohen's d and partial correlation effect sizes for each of the DK atlas regions were performed using R (version 3.2.2) metafor package (version 1.9-7) (56). False discovery rate (FDR) ($p_{FDR} < .05$) (57) was used to control for multiple comparisons. Cortical maps depict significant effect sizes ($p_{FDR} < .05$) overlaid on (metallic gray) cortical surface models (https://brainder.org/research/brain-for-blender). Possible confounding effects of differences in parental socioeconomic status on group differences were examined using subsample analyses (see Results SR3, Figures, and Tables S8a and S9b, and S52a and S53b in Supplement 1). Effects of FreeSurfer version and scanner field strength were examined using meta-regressions (Supplement 1).

RESULTS

Widespread Thinner Cortex With Regional Specificity in Schizophrenia

Individuals with schizophrenia, compared with healthy volunteers, showed widespread significantly thinner cortex in all DK atlas regions except the bilateral pericalcarine region (model A), with effect sizes between Cohen's $d = -0.536$ (right fusiform gyrus) and Cohen's $d = -0.077$ (left pericalcarine fissure) and marginal (least square) mean thickness differences between −3.33% (left parahippocampal gyrus) and −0.45% (left pericalcarine fissure) (Figure 1A and Table S4a in Supplement 1). The largest negative effect sizes (Cohen's $d < -0.40$) were observed for left/right hemisphere (Cohen's $d = -0.530/-0.516$); bilateral fusiform, temporal (inferior,

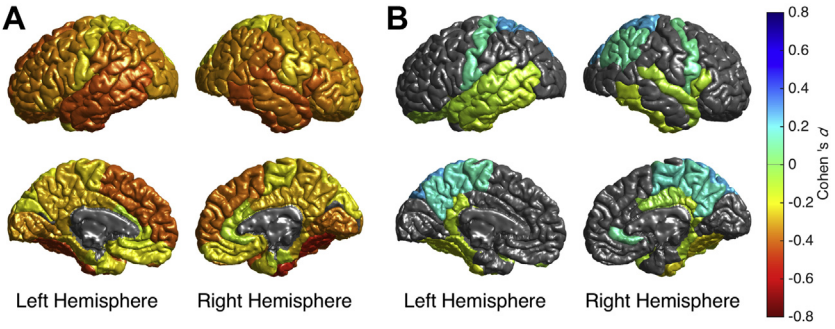

Figure 1. Cortical map of regional Cohen's d effect sizes for schizophrenia subjects' vs. healthy volunteers' cortical thickness contrast statistically controlling for age and gender **(A)** and age, gender, and global cortical thickness **(B)**. Only regions with $p_{false\ discovery\ rate} < .05$ are depicted in color. In panel **(B)**, warm colors (yellow-red) reflect regions in which the effect of schizophrenia is more than the mean global cortical thinning, and cool colors (green-blue) reflect regions where the effect of schizophrenia is less than the mean global thinning compared with healthy volunteers.

middle, and superior), and left superior frontal gyri; right pars opercularis; and bilateral insula.

In the context of widespread thinner cortex in schizophrenia, we assessed regional specificity of these cortical thickness differences. When controlling for individual differences in global mean cortical thickness, several regions showed significantly thinner cortex (e.g., fusiform, parahippocampal, inferior temporal gyri), whereas other regions showed significantly thicker cortex (e.g., superior parietal cortex, precuneus, paracentral lobule) in individuals with schizophrenia compared with healthy volunteers (model B) (Figures 1B and Figure 2; Table S4b in Supplement 1). These findings suggest regional specificity of thinner cortex in schizophrenia.

Widespread Smaller Cortical Surface Area Without Regional Specificity in Schizophrenia

Individuals with schizophrenia, compared with healthy individuals, showed widespread significantly smaller cortical surface area in all DK atlas regions except the bilateral isthmus cingulate region (model A), with effect sizes between Cohen's $d = -0.254$ (mean right hemisphere) and Cohen's $d = -0.040$ (right isthmus cingulate) and marginal (least square) mean surface area differences between −3.39% (left rostral anterior cingulate) and −0.55% (right isthmus cingulate) (Figure 3A; Table S5a in Supplement 1). The largest effect sizes (Cohen's $d < -0.20$) were observed for left (Cohen's $d = -0.251$) and right (Cohen's $d = -0.254$) hemisphere and bilateral superior frontal, fusiform, inferior and middle temporal, and right precentral gyri.

In the context of widespread smaller cortical surface area in schizophrenia, we assessed regional specificity of these cortical surface area differences. When controlling for individual differences in total cortical surface area, no regions showed significantly smaller surface area, whereas three regions showed significantly larger cortical surface area (bilateral isthmus cingulate, precuneus, and left paracentral) in individuals with schizophrenia compared with healthy volunteers (model B) (Figure 3B; Table S5b in Supplement 1). These findings suggest that smaller cortical surface area is predominantly global in schizophrenia except for the three regions noted, which appear less affected.

Group-by-Gender Interactions

No significant group-by-gender interactions were detected for either cortical thickness or surface area for any of the DK atlas regions (Tables S6 and S7 in Supplement 1).

Group-by-Age Interactions

There were significant group-by-age interactions for both left ($p_{FDR} = .007$) and right ($p_{FDR} = .01$) temporal pole thickness, with individuals with schizophrenia showing stronger negative correlations with age (left, $r = -.13$, $p_{FDR} = 1.51E\text{-}13$; right, $r = -.12$, $p_{FDR} = 1.55E\text{-}07$) than healthy volunteers (left, $r = -.05$, $p_{FDR} = .02$; right, $r = -.04$, $p_{FDR} = .03$). These interactions remained significant even when controlling for global mean cortical thickness (Figure S2 and Tables S8a, S8b, S10, and S11 in Supplement 1). There were no significant group-by-age interactions for cortical surface area for any of the DK atlas regions (Table S9 in Supplement 1).

Partial Correlations With Age of Onset and Duration of Illness

Earlier age of onset ($r = .063$, $p_{FDR} = .03$) and longer duration of illness ($r = -.061$, $p_{FDR} = .04$) were significantly correlated with thinner right insula cortical thickness (Tables S33 and S34 and Figure S3 in Supplement 1). There were no significant correlations between age of onset or duration of illness and cortical surface area for any of the DK atlas regions (Tables S43 and S44 in Supplement 1).

Effects of Antipsychotic Medications on Cortical Thickness

Effect sizes comparing left and right hemisphere cortical thickness from individuals with schizophrenia on no

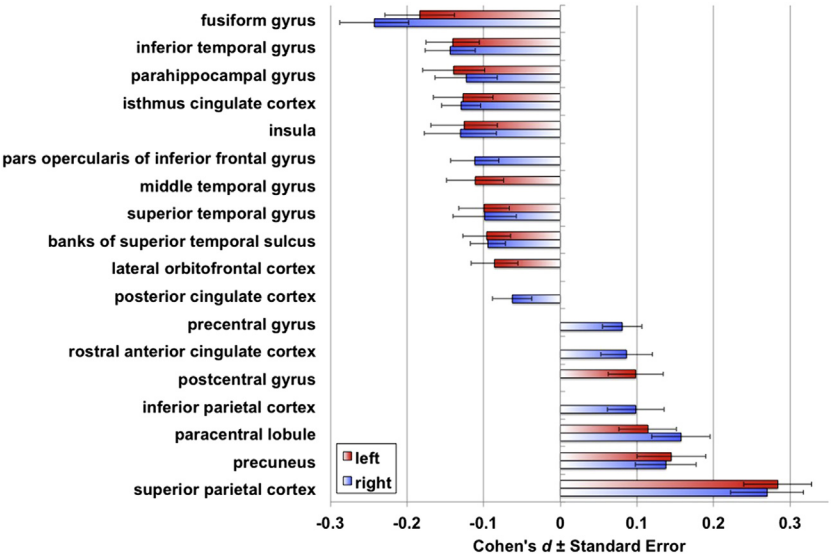

Figure 2. Cohen's *d* effect sizes for schizophrenia subjects' vs. healthy volunteers' cortical thickness contrast statistically controlling for age, gender, and global mean cortical thickness. Only regions with $p_{false\ discovery\ rate} < .05$ are depicted in color.

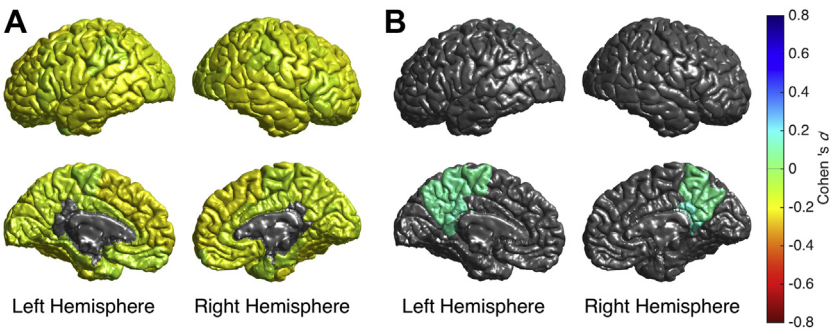

Figure 3. Cortical map of regional Cohen's *d* effect sizes for schizophrenia subjects vs. healthy volunteers' cortical surface area contrast statistically controlling for age and gender **(A)** and age, gender, and total cortical surface area **(B)**. Only regions with $p_{false\ discovery\ rate} < .05$ are depicted in color. In panel **(B)**, warm colors (yellow-red) reflect regions in which the effect of schizophrenia is more than the mean lower surface area, and cool colors (green-blue) reflect regions where the effect of schizophrenia is less than the mean lower global surface area compared with healthy volunteers.

(unmedicated; left/right, Cohen's $d = -0.275/-0.278$), second-generation (left/right, Cohen's $d = -0.536/-0.516$), first-generation (left/right, Cohen's $d = -0.765/-0.648$), or both second-generation and first-generation (left/right Cohen's $d = -0.770/-0.704$) antipsychotic medications with healthy volunteers were significant for all but the unmedicated group ($p_{FDR} > .05$) (Figure 4; Tables S12–S15 in Supplement 1).

Groupwise comparisons of left and right hemisphere thickness found nominally significant effects for all medicated versus unmedicated groups (Figure 4; Tables S16–S18 in Supplement 1). Similarly, nominally significant effects were found for first-generation versus second-generation and both second-generation and first-generation versus second-generation medication groups, but not both versus first-generation medication groups (Figure 4; Tables S19–S21 in Supplement 1). No significant regional effects were observed for the last four group contrasts ($p_{FDR} > .05$) (Tables S18–S21 in Supplement 1). For detailed regional effects of antipsychotic medications on cortical thickness and surface area, see Results SR1 in Supplement 1.

Partial Correlations With Medication Dose

Higher chlorpromazine dose equivalents were significantly correlated with thinner cortex in almost all the DK atlas regions except bilateral entorhinal and pericalcarine cortex; bilateral lingual and transverse temporal gyri; left postcentral, cuneus, and parahippocampal gyri; caudal anterior cingulate cortex; right superior parietal and rostral anterior cingulate cortex; and right frontal pole (Figure S6A and Table S32 in Supplement 1). The correlations were significant for both left ($r = -.126$) and right ($r = -.126$) hemisphere thickness and were strongest (partial $r < -.10$) for left ($r = -.166$) and right ($r = -.148$) superior frontal, left ($r = -.113$) and right ($r = -.108$) middle temporal, left ($r = -.112$) and right ($r = -.106$) superior temporal, right inferior temporal ($r = -.113$), right pars triangularis of inferior frontal ($r = -.113$), left ($r = -0.102$) and right ($r = -.108$) caudal middle frontal, and left supramarginal ($r = -.103$) gyri.

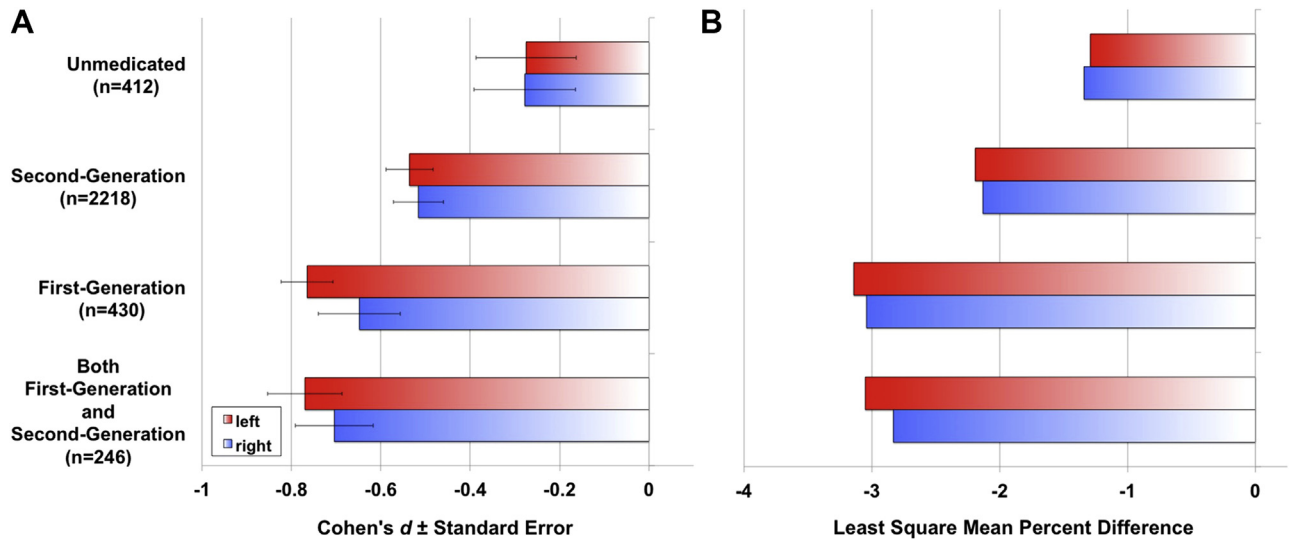

Figure 4. Cohen's *d* effect sizes **(A)** and least square mean percent difference **(B)** for schizophrenia subjects vs. healthy volunteers contrasts in global cortical thickness statistically controlling for age and gender by medication group and hemisphere. Nominal one-tailed *p* values for left and right hemisphere thickness group comparisons statistically controlling for age and gender were as follows: second-generation vs. unmedicated (left, $p < .05$; right, $p < .06$); first-generation vs. unmedicated (left, $p < .01$; right, $p < .002$); both first-generation and second-generation vs. unmedicated (left, $p < .02$; right, $p < .05$); first-generation vs. second-generation (left, $p < .03$; right, $p < .03$); both first-generation and second-generation vs. second-generation (left, $p < .02$; right, $p < .05$); both first-generation and second-generation vs. first-generation (left, $p = .50$; right, $p = .48$) (Tables S16–S21 in Supplement 1).

Importantly, post hoc analysis showed that higher chlorpromazine dose equivalents were significantly correlated with thinner cortex even when controlling for negative symptom severity (Table S41 and Figure S7 in Supplement 1). There were no detectable correlations between chlorpromazine dose equivalents and cortical surface area for any of the DK atlas regions (Table S42 in Supplement 1).

Partial Correlations With Symptom Severity Scores

Higher PANSS total and positive symptom severity scores were significantly correlated with regional thinner cortex (Figure S6B, Table S35, Figure S6D, and Table S36 in Supplement 1), whereas higher PANSS negative symptom scores were significantly correlated with widespread thinner cortex in left ($r = -.085$) and right ($r = -.089$) hemispheres (Figure S6C and Table S37 in Supplement 1; see Results SR2 in Supplement 1 for details). PANSS total, positive, and negative symptom severity scores were not significantly correlated with regional cortical surface area for any of the DK atlas regions (Tables S45–S47 in Supplement 1).

DISCUSSION

The main findings of this study are that individuals with schizophrenia, compared with healthy volunteers, show the following: 1) widespread thinner cortex (left/right, Cohen's $d = -0.530/-0.516$); 2) widespread smaller cortical surface area, about half the size of the effect observed for cortical thickness (left/right Cohen's $d = -0.251/-0.254$); 3) the largest effect sizes in frontal and temporal lobe regions for both measures, with regional specificity for cortical thickness, but not cortical surface area (based on the analyses controlling for global thickness and surface area); 4) approximately two times larger negative cortical thickness effect size when on second-generation antipsychotic medications (left/right, Cohen's $d = -0.536/-0.516$) and approximately three times larger cortical thickness effect size when on first-generation (left/right, Cohen's $d = -0.765/-0.648$) or both first-generation and second-generation (left/right, Cohen's $d = -0.770/-0.704$) antipsychotic medications relative to unmedicated individuals with schizophrenia (left/right, Cohen's $d = -0.275/-0.278$); and 5) a stronger negative correlation between age and bilateral temporal pole cortical thickness (left, $r = -.13$ vs. $r = -.05$; right, $r = -.12$ vs. $r = -.04$). With regard to partial correlations with clinical variables, 6) earlier age at onset and longer duration of illness were associated with thinner insula cortex; 7) standardized medication dose (chlorpromazine dose equivalent) and 8) negative symptom severity were associated with widespread thinner cortex; and 9) total and 10) positive symptom severity were associated with regional thinner cortex. Most observed correlations were small ($r < .2$). Moreover, despite the high power to detect small effects, medication use and other clinical variables were not significantly associated with cortical surface area.

These findings are consistent with the interpretation that the thinner cortex observed in individuals with schizophrenia shows regional specificity and is associated with the disease (28–30), its severity (43–48), and antipsychotic medication treatment (49–51), with a larger effect for first-generation compared with second-generation antipsychotic medications (16,58–60). We cannot fully exclude the possibility that observed medication effects on cortical thickness are partially due to group differences in age or duration of illness (61), which also show patterns of increase across the groups. However, such an interpretation is rendered unlikely by the facts that 1) age was statistically controlled for in the medication type analyses; 2) duration of illness, which is highly collinear with age, showed effects above and beyond age only on right insula thickness; 3) there was only a group-by-age interaction on temporal pole thickness (while medication effects were widespread); and 4) meta-regressions showed no effects of age or duration of illness on group contrast effect sizes (see Results SR1 in Supplement 1). Furthermore, dissociating medication effects from other potentially confounding variables requires well-powered, first-episode longitudinal studies, preferably with random assignment to first-generation or second-generation antipsychotics. Two longitudinal imaging studies that randomly assigned individuals to medication treatments found significant gray matter reductions for haloperidol but not olanzapine (58,62); these findings are consistent with our meta-analysis and with reported medication effects on cortical thickness in rodents (63).

None of the other potential confounding variables, including gender distribution, age at onset, medication dose, global symptoms, negative symptoms, or positive symptoms, showed a pattern consistent with the observed medication effects. These variables are therefore unlikely to explain the differences in cortical thickness effect sizes across the antipsychotic medication groups on their own, although more complex interactions could exist. In contrast to thinner cortex, smaller cortical surface area in individuals with schizophrenia appears to be a more global phenomenon associated with the disease, but not with its severity or its treatment. It is possible that more focal cortical surface area effects are obfuscated through the averaging of measurements within DK atlas regions; vertexwise analyses may have higher power for detecting and localizing such effects.

This study found significant group-by-age interactions on cortical thickness in the bilateral temporal pole regions only, with a stronger negative correlation between age and cortical thickness in individuals with schizophrenia than in healthy volunteers. In addition, this study found that earlier age at onset and longer duration of illness were associated with thinner cortical thickness in the insula only. These findings corroborate reported longitudinal findings of lower cortical volumes at illness onset as well as progressive volume decline in the temporal pole and insula in individuals with schizophrenia (64,65) and individuals at ultra-high risk for psychosis (66). Given our results, these volume declines may reflect cortical thinning rather than cortical surface area reduction. While our findings may suggest that there are few differential effects of age on cortical thickness between individuals with schizophrenia and healthy volunteers, we must keep in mind that age effects on thickness across a large age range are nonlinear (67) and that this meta-analysis combines linear age effects across multiple independent cross-sectional cohorts of various ages. Longitudinal studies are better poised to address the question of differential effects of age and duration of illness on cortical thickness in schizophrenia, and some have observed steeper rates of cortical thinning in multiple regions

in individuals with schizophrenia and their non-ill co-twins (61). ENIGMA Schizophrenia Working Group members are actively working on pooling longitudinal studies for a meta-analysis to further address these questions.

Taken together, these findings may suggest that cortical surface area developmental trajectories in psychosis may be predominantly influenced by early neurodevelopmental, perhaps predominantly genetic, factors. In contrast, cortical thickness, in addition to likely being influenced by different genes (13,14), may be more plastic and also influenced by additional environmental and neurodegenerative factors (e.g., treatment, cannabis use, age) (68).

This study found significant widespread associations between standardized medication doses (chlorpromazine equivalents) and cortical thickness but not cortical surface area. This finding is consistent with and extends a prior meta-regression analysis, which reported that higher medication doses are associated with smaller gray matter volume (51). Given our results, the association with volume is likely due to cortical thickness rather than surface area. The finding is also consistent with the larger effect sizes for individuals with schizophrenia who were on antipsychotic medications compared with individuals who were not. An alternative interpretation may be that more severely ill patients receive higher doses of medication given the observed significant associations between symptom severity and regional cortical thickness. However, consistent with medication dose effects on cortical thickness, we found that significant associations between chlorpromazine dose equivalent and cortical thickness were still observed in post hoc partial correlation analyses that statistically controlled for negative symptom severity. In this analysis, we opted to control for negative rather than positive symptom severity, as negative symptoms tend to be less influenced by medication dose than positive symptoms.

We caution that the likelihood that antipsychotic medications are associated with thinner cortex in individuals with schizophrenia should by no means be interpreted as a contraindication for their use in treating patients with severe mental illnesses, including schizophrenia. In fact, a recent study found that medication treatment was associated with thinner cortex and better behavioral performance on a cognitive control task (26% higher d′-context score) (24). Most importantly, antipsychotic medications tend to successfully treat severely debilitating psychotic symptoms, reduce relapse risk following a first-episode break (69), and reduce suicide risk (70). As such, they play a critical role in the treatment of psychosis.

Similar published meta-analyses in bipolar disorder and major depressive disorder, with the same study design and analytical methods, found thinner bilateral frontal, temporal, and parietal lobe cortex in individuals with bipolar disorder with evidence for divergent effects of medication treatments (71) and thinner regional cortex in adults with major depressive disorder and smaller total and regional cortical surface area in adolescents with major depressive disorder (72). Taken together, these very-large-scale studies suggest both similarities and differences in cortical abnormalities observed among these three major psychiatric illnesses.

To our knowledge, this is the first meta-analysis of cortical thickness and surface area abnormalities in schizophrenia. Only one other schizophrenia study has provided a comprehensive listing of Cohen's *d* effect sizes for regional cortical thickness abnormalities comparing individuals with schizophrenia, non-ill first-degree relatives, and healthy volunteers (1).

The major strength of the study is its large sample size, which provides sufficient power to detect even small effects (e.g., symptom associations). Weaknesses include the following: 1) the group of unmedicated individuals with schizophrenia does not distinguish never-medicated from unmedicated at time of scan, leaving effect sizes for medication-naïve subjects to be determined; 2) despite the large total sample size, many regional thickness differences between medication subgroups did not survive multiple comparison correction; 3) this study does not examine possible group differences in brain lateralization, though such analyses will be reported on separately; and 4) the analysis of chlorpromazine equivalents did not dissociate first-generation and second-generation antipsychotic medications, which may have dissociable effects on cortical thickness (51,72). Finally, while this meta-analysis is unique in that it standardized image analysis methods across sites, any meta-analysis, including this one, is limited by sources of variation inherent to the analysis of retrospectively collected samples that cannot be fully controlled for. Sample differences include the use of different scanners and different assessments or processes to arrive at diagnosis, age at onset, duration of illness, medication dose and adherence, etc. Meta-analyses control for these differences by summing within-site effects across sites, providing generalized mean effect sizes. Similar to other meta-analyses, this meta-analysis does not control for all variance in assessments that can lower power to detect effects.

Taken together, the findings from this meta-analysis suggest that thinner cortex in schizophrenia shows regional specificity and is affected by the illness, its severity, and treatments with antipsychotic medications, whereas smaller cortical surface area is mainly influenced by widespread effects of the illness possibly mainly influenced by developmental processes. In the context of ENIGMA, these findings suggest that schizophrenia genetic association studies employing cortical thickness as a quantitative trait may need to control for medication effects, whereas studies that employ cortical surface area as a quantitative trait may not need to control for medication effects.

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